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CURRENT TRENDS IN BIOLOGIC PRODUCTS*

LIEUTENANT COLONEL ELLIOTT S. ROBINSON, M.C., A.U.S.†

THE following remarks on current trends in biologic products, not being based on a careful survey of current literature or opinion, represent only an expression of the impressions gained through some years of intimate contact with the manufacture of biologic products. Had there been more opportunity for painstaking study and preparation, the comments to be made might have undergone some alteration and doubtless would have greater value; but in these days, time for leisurely consideration has for many people joined those things that have essentially ceased to exist.

Current trends are discernible only against the background of what has happened in the past. For this reason, it is desirable not only to consider what is going on now and what was being done two or three years ago but to go farther back as well, if one is to see clearly how present thoughts and practices have developed and how they differ from those of earlier years. It will also be helpful if the large field of biologic products is divided into smaller portions, namely, antiserums, — both prophylactic and therapeutic, — vaccines — both bacterial and viral — and toxoids.

The development of antiserums, practically speaking, began with the discovery of diphtheria antitoxin in the 'nineties. The early antitoxins were not highly potent, and the doses required were relatively large. The quality too appears to have been more or less unreliable, and it was in the hope of providing more potent antitoxin that the Massachusetts Antitoxin Laboratory was established. For a number of years the chief improvement was in the direction of increasing the number of units of antitoxin per unit volume, thus reducing the volume required to provide a given dose. This was largely a matter of improvement in methods of toxin production and of immunization of horses.

The next step in development was the discovery that the antitoxic property is not associated with all the constituents of horse serum but only with the globulin fraction. This globulin can be separated by treatment of the serum or plasma with ammonium or sodium sulfate, and the salt subsequently removed from the precipitated globulin by dialysis. At their best, these methods result in a reduction of volume of the original serum of the order of eight- to tenfold and an increase in potency of the order of fivefold. This was an important development, for it permitted the administration of much larger doses and undoubtedly saved additional lives. It also led to some reduction in the incidence of serum sickness.

The next advance was not realized for a number of years, although it was discovered within ten years or less of the salting-out methods just described. This advance was the digestion method, brought to practical usefulness by Parfentjef, in which the plasma or serum is subjected to digestion by proteolytic enzymes. The antitoxic globulins are less susceptible to the action of the enzymes than are the other protein constituents of the serum, and their specific activity is not altered provided the enzymes are not allowed to act too long or too vigorously. The final product is often water-clear, and the activity per unit volume is high, permitting the administration of large doses in small volume. Serum sickness following the use of these products is infrequent.

The antibacterial serums have had a somewhat different course of development because of fundamental differences between the two varieties of serum. Prior to 1916, little had been accomplished in the development of antibacterial serums, but at about that time considerable success was achieved in the production of antimeningococcus serum and Type I pneumococcus antiserum. Both these were produced by the injection of horses with the appropriate bacteria. After a time, usually a number of months, the serum of the animals contained protective antibody in such concentration as to be useful therapeutically. Although antimeningococcus serum rapidly gained a recognized place as a useful therapeutic agent, antipneumococcus serum did not, because it was useful against only one type of infection, and also because the volume that it was necessary to administer practically limited its use to large and well-equipped hospitals.

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†Assistant professor of applied immunology, Harvard Medical School, and director, Division of Biologic Laboratories, Massachusetts Department of Public Health (on leave of absence).

In 1924, Felton published the first of a series of studies that marked the next stage in the development of antipneumococcus serum in particular and antibacterial serums in general. He worked on methods of antibody concentration, using sulfate precipitation and also precipitation by means of alcohol. The success of his work led to the widespread use of antipneumococcus serum, which was fostered by the development of statewide pneumonia-control programs. The history of these is too well known to warrant further discussion here, except to recall the leading role played by the Massachusetts Department of Public Health.

At the same time, Felton conducted extensive studies on methods of testing the potency of antipneumococcus serum. In the long run, this may prove to have been the more important contribution, for it focused attention on the difficulties involved in reasonably accurate bioassay of antibacterial serums, which in turn has led to more critical evaluation of the tests employed for other biologic products.

The next marked departure from previous practice was a change in the source of serum. With minor exceptions, the horse was for many years the main source of serums for human use, and this animal has several outstanding advantages for the purpose. Goodner in 1937 announced that more potent antipneumococcus serum could be produced in rabbits and proposed that these animals be substituted for horses. It was also claimed that the rabbit antibody (globulin) was of a smaller molecular size than the corresponding horse antibody, and that this characteristic should increase its ability to penetrate into pneumonic lesions. In my opinion, there has been no clear evidence that, unit for unit, rabbit serum gives better results than horse serum; but the switch to rabbits markedly increased the feasibility of producing serums for the less frequently occurring types of pneumococcal infection, and made possible the production and trial of other serums for which the demand is not great enough to warrant the use of horses.

Prior to the heyday of antipneumococcus serum, the intravenous administration of serums was not widely practiced, and little attention was paid to the occurrence of thermal reactions following intravenous serum therapy. These reactions, however, were of such frequency following the administration of antipneumococcus serum that they became a cause of grave concern, for they were often unpleasant and occasionally lethal. It now appears to be generally conceded that such reactions are produced by specific reaction-producing substances that are referred to as pyrogens. The exact nature of pyrogens does not seem to be clearly settled, although they are widely believed to be, and probably are, extraneous bacterial protein that is introduced into the serum in the process of manufacture. The method of introduction is sometimes obscure, but scrupulous cleanliness and the use of pyrogen-free water in manufacturing processes seem to decrease markedly or to eliminate the occurrence of thermal reactions.

At the moment the current trend of antibacterial serums for therapeutic purposes is toward oblivion. The introduction of the sulfonamides and penicillin and their demonstrated effectiveness restrict the potential field of usefulness of serums largely to cases in which infection is due to drug-resistant bacterial strains or the patient is drug sensitive. This field is apparently small, much smaller in fact than some authorities feared during the early years of sulfonamide therapy.

Deserving of separate mention is the development of large-scale production of human blood and its fractions. It is important not only in itself but also because the methods developed will doubtless find application in the production of immune serums of animal origin. This development has been so recent, and is so well known that only the high lights and their probable effect on other biologic products need be mentioned here. The first step was the discovery that whole blood can be stored for limited periods for use in emergency transfusions. This was a justifiable but to some extent a wasteful procedure until it was learned that the blood cells can be discarded toward the end of the period of storage and the remaining plasma kept for a somewhat longer time. With the advent of war, the demand for plasma increased tremendously, but the difficulties of storing it in reasonably permanent form were considerable. These were overcome by storage as dried plasma, which was prepared by freezing the liquid plasma and removing the water by evaporation in vacuo. This has proved to be a highly satisfactory preparation for military use.

Just as only a relatively small portion of the serum carries antibodies, so too only a portion of the blood protein — in this case, the albumin — is of great importance in the treatment of shock. Exception can doubtless be taken to this opinion, but there was at any rate sufficient evidence to warrant the investigations undertaken under the direction of Cohn at Harvard to separate the albumin. These led first to the successful large-scale preparation of concentrated albumin solutions that in much smaller volume than plasma had an equivalent osmotic effect.

The methods used, with appropriate modification, have been employed for the separation of other serum-protein fractions. From the public-health standpoint, the most important is the gamma globulin, for this carries the naturally occurring antibodies. At present the most conspicuously useful of these is the antibody against measles. Extensive experiments have shown that human gamma globulin protects children who have been exposed to measles and can be used to modify the disease in such children. Other uses will doubtless be found, but this one alone is of considerable importance.

Let us turn our attention to the field of prevention, which, from the public-health viewpoint, is of greater interest, and first consider bacterial vaccines. Typhoid vaccine may be taken as an example, for it has been extensively studied and used and is of great importance to public-health and military medicine. Starting with its optional use in the British Army and its later adoption for compulsory use in the American Army in 1911, its value was conclusively demonstrated during World War I. The low incidence of typhoid fever in the Army during the years following the war made for a feeling of complacent acceptance of the value of typhoid vaccine, but this confidence was badly jarred by Grinnell's work at Harvard. He showed by experiments on mice and with human volunteers that the Rawlings strain ordinarily used for vaccine production was not particularly effective in producing active immunity in the mice or protective antibody in the human volunteers. This failure was associated with a loss of virulence of the Rawlings strain, probably the result of prolonged cultivation; for vaccines made from recently isolated typhoid strains were definitely superior both in mice and in human subjects. Moreoever, a virulent Rawlings strain produced by mouse passage was of distinct immunizing value when used for vaccine production. Grinnell's recommendation of the use of a virulent strain was promptly adopted by the Massachusetts Antitoxin and Vaccine Laboratory. His experiments were confirmed on a large scale by the Army Medical School. His recommendations have for some time been generally accepted, and have been incorporated into current practice with respect to most bacterial vaccines.

A useful bacterial vaccine must be effective and must be safe. Effectiveness seems to be most nearly achieved when the bacterial antigen is present in the form found in the living bacterium. The use of a live bacterial vaccine violates the requirement of safety, so that methods of killing the bacteria must be used that will alter as little as possible the character of the bacterial antigen. For many years heat has usually been relied on for this purpose, although chemicals have been employed more or less widely. Recently irradiation with ultraviolet light has been studied, and to some extent this appears to be more promising than any other measure yet devised. Regardless of the method employed with whole-organism vaccines, it is believed that no more than the minimum dose effective for killing should be used; and even this may be enough to affect the antigen more or less deleteriously.

An entirely different approach to the problem of vaccine production is the attempt to isolate the antigen from the bacterial cell by chemical methods. This is undoubtedly the method most to be desired, for theoretically it provides pure antigenic substance free of extraneous material, and permits determination of dosage in terms of weight of the pure substance without the necessity for resort to more or less cumbersome bioassays. Furthermore, the pure antigens are probably more stable, at least in concentrated or dry form, than are the corresponding bacterial suspensions. Success in isolating more or less pure antigens has been attained in the case of the typhoid bacillus and, more conspicuously, with the pneumococcus, although in neither instance has the antigen been widely adopted for use. It seems likely, however, that further development of vaccines will follow along this line.

It might have been appropriate to begin the discussion of vaccines with those made from viruses, since historically a virus vaccine — that protecting against smallpox — was the first to be generally used. This particular vaccine, however, has undergone very little change in recent years, and except for relatively minor technical improvements is made essentially as it was forty or more years ago. Smallpox vaccine is obtained by the inoculation of the skin of calves with vaccinia virus and subsequent harvesting of the resultant vesicles. Rabies vaccine is obtained by propagating the virus in rabbits and removing the spinal cords, rich in virus, when the animal shows pronounced symptoms of the disease. Other viruses, too, could for many years be propagated only by inoculation of susceptible animals; and if vaccines were to be made they must represent suspensions of the appropriate animal tissues. For some of the virus diseases, such as chicken pox, vaccination would hardly seem worth while even if it were available, for these particular diseases are usually mild; and for others, no suitable susceptible animal is known.

The most striking advance in recent years was the discovery that many viruses can be grown in chick embryos. The most favorable site and time of inoculation and the part of the embryo in which the virus develops most luxuriantly depend on the particular virus. Although many viruses and rickettsias can be grown in this way, some cannot, so that it is still not possible to develop a vaccine against any and every type of virus. The most extensively used of the chick-embryo vaccines are those for yellow fever and for louse-borne (epidemic) typhus fever. Both these vaccines have been used on a large scale by the Army as well as in civilian groups, and the results have been excellent. There is also in preparation a vaccine against influenza, Types A and B, which it is hoped to have available for military use in the event of an outbreak of influenza. It is to be expected that similar vaccines against other diseases due to viruses will come into more or less extensive use, for there are strong indications that they will have value. Some of these diseases, such as St. Louis encephalitis, are relatively rare, so that vaccines against them may not be widely used even if they become available.

One thing that may curtail the use of vaccines derived from chick embryos is the possible develop-

ment of egg sensitivity in persons inoculated with these vaccines. The possibility of its occurrence has been noted and a case report has been published, but there has so far been little in Army experience to indicate that this is a serious danger. It should not be overlooked, however, that the danger might be increased if the use of such vaccines became general or were extended to the younger age groups.

Another group of prophylactic biologic products deserving of mention comprises the toxoids. Bacterial toxins are ordinarily too poisonous to permit their use as antigens in human beings, the permissible doses being too small to be effective. This is conspicuously true in the case of diphtheria and tetanus. It is relatively easy to destroy their toxicity with formaldehyde without any great destruction of antigenic efficiency. Diphtheria toxoid prepared in this way came into general use in this country in about 1930. The fact that three doses were ordinarily required to produce satisfactory levels of immunity led to the adoption of toxoid precipitated on alum. Not only is such a precipitate a more effective antigen than the unprecipitated toxoid, but the process also eliminates extraneous constituents of the basic material.

Although toxoids are in general reasonably free from undesirable side reactions, diphtheria toxoid and, less frequently, tetanus toxoid may give rise to marked but transient local or general reactions. It has also been found that tetanus toxoid may give rise to reactions of the anaphylactic type, but this difficulty was definitively traced to the use of certain peptones in the medium in which the toxin was produced. These reactions stimulated interest in the use of mediums of known chemical constitution for toxin production, for such mediums contain only substances of relatively low molecular weight and are therefore nonantigenic. The first successful step in this direction was the adaptation by Pappenheimer at the Antitoxin and Vaccine Laboratory of the medium devised by Mueller at Harvard for the growth of diphtheria bacilli. This medium has been in routine use for several years and has yielded high-grade toxin of uniform quality. Equally successful results have not been obtained with tetanus toxin production, but advances have been made. It is undoubtedly in this direction that further improvements will follow.

An outgrowth of the production of diphtheria toxin on a medium of known composition was the isolation of essentially pure diphtheria toxin by Pappenheimer. This was previously done by Eaton, but there was uncertainty of his complete success because of the complex nature of the medium. Actually, Eaton's preparations were excellent. The use of toxoids made from pure toxins has not as yet been practically applied, for the ordinary commercial preparations of both diphtheria and tetanus toxoid have been in general quite satisfactory; but the possibility of using pure preparations is one that may in the future become of increasing importance.

One other trend in current practice is worth mentioning. So many definitely useful prophylactic agents are now available that innumerable injections would be given if advantage were taken of all of them. Therefore a number of combined preparations have been proposed, and several have been more or less generally adopted. Diphtheria and tetanus toxoid together or mixed with pertussis vaccine have been employed in pediatric practice, and a combination of tetanus toxoid with typhoid-paratyphoid vaccine has found some favor for military use. Opinion has at times been divided concerning the efficacy of antigens simultaneously administered, but there seems to be little difference between the results from giving them separately and giving them together, at least when the number of antigens is limited to two or three. The use of such combinations may be expected to increase.

Since this is a celebration of the fiftieth anniversary of the Antitoxin and Vaccine Laboratory as well as of the seventy-fifth anniversary of the Department of Public Health, I should like in closing to call attention to the fact that the laboratory has played a not inconsiderable part in shaping the trends that have been described. This has been possible largely because of the close association of the laboratory with the other scientific institutions in Boston, notably with the Harvard Medical School. Nowhere in this country is there the favorable situation existing here, with a state laboratory actively engaged in the manufacture of biologic products located so close to first-rate medical schools. Let us hope that the future will see the continuance of this mutually profitable association.

ENGINEERS AND ENGINEERING IN THE MASSACHUSETTS STATE BOARD OF HEALTH*

GORDON M. FAIR†

CAMBRIDGE, MASSACHUSETTS

THE story of public health in its modern implications, like that of other great social reforms, is the story of great men whose convictions and leadership, wisdom and toil, temporary failure and ultimate success fashioned a pattern of public opinion that could not be denied and that has left its imprint on a century of human existence.

The public-health movement as it is seen today had its roots in the Industrial Revolution of the nineteenth century. Industry, the child of scientific discovery and invention, created the opportunity for mass employment. In the early stages of industrial development, limitations on the transmission of power and the need for a nearby labor market forced the herding together of people in houses that clustered about the factories. To meet the rapid influx of workers, these mushrooming communities often could not expand their facilities fast enough to satisfy new and often frightening sanitary needs. In particular did the need for more abundant distribution of water, for more effective disposal of human wastes and for more adequate housing force itself on the attention of thoughtful men whose duties, associations or interests brought them into contact with the suffering of the masses of the people.

We can understand, therefore, why engineers were engaged from the very beginning in the modern public-health campaign. The example for so doing was set in England during the great sanitary awakening of the middle-nineteenth century. There Sir Robert Rawlinson was employed by the General Board of Health in 1848 as superintendent inspector, and in this capacity conducted the engineering studies necessary for the construction of sanitary works in growing industrial Britain. The real genius of British public health and the originator of many of its engineering advances, however, was Sir Edwin Chadwick. There is no gainsaying that the main threads of public-health progress in Great Britain tie back to him. In the United States, these threads, too, can be traced to a single man, Lemuel Shattuck, like Chadwick neither a physician nor an engineer, but an enthusiast for sanitation. What Shattuck[1] reports a London periodical of December, 1849, as saying about Chadwick would seem to apply equally well to Shattuck himself:

> He was not a man of varied or profound attainments, nor distinguished by any extraordinary brilliancy of intellect. But he was remarkable for his sagacity in extracting from masses of detail the master facts, and bringing these to bear for the elucidation of a master thought. He would confront, undaunted, any amount of intellectual labor, exploring mountains of blue books and statistical returns till he had fully ascertained and brought to light their true riches.

Shattuck's "Report of a General Plan for the Promotion of Public and Personal Health" was presented to the General Court of Massachusetts on April 25, 1850. His conclusions were based on intensive studies of the sanitary movements abroad and at home. Because of the similarity in social background of the two countries, British experience, above all, influenced Shattuck's plan for a sanitary survey of the Commonwealth. Among the measures advocated in this plan were the establishment of a general board of health, composed so far as practicable "of two physicians, one counsellor-at-law, one chemist or natural philosopher, one civil engineer, and two persons of other professions or occupations; all properly qualified for the office by their talents, their education, their experience and their wisdom."[2] Two reasons were given why the members should not be selected exclusively from one profession. In the first place, Shattuck anticipated that numerous questions, requiring a knowledge possessed by different professions, would be presented for discussion and decision. Second, the promotion of public health, in Shattuck's mind, was a matter that concerned every profession and every person. The services of medical men were indispensable, but the services of other professions, and of every person in their respective spheres, must be put in requisition before reform could be complete.

The civil-engineer member of the proposed board, Shattuck[3] suggested, should possess "competent knowledge to determine the best methods of planning and constructing public works, and the best architectural sanitary arrangements of public buildings, workshops and private dwelling-houses."

Although nineteen years elapsed before the Massachusetts State Board of Health was established and five more before John C. Hoadley, of Lawrence, was appointed engineer member of the board, this recommendation of Lemuel Shattuck's seems to be the American wellspring of engineers in public health. About Hoadley, who served from 1874 to 1882, it is known that he began his career as a civil engineer on the enlargement of the Erie Canal and was later placed in charge of locating, constructing and installing textile mills in Massachusetts. In the course of time, his work with textile machinery turned him away from the field of civil engineering to that of mechanical engineering, in

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†Abbott and James Lawrence Professor of Engineering, and Gordon McKay Professor of Sanitary Engineering, Harvard University.

which he became expert. This shift in interest may explain why he did not provide the engineering leadership that he might have exerted in the new board. An examination of the scientific articles and reports published in the regular series of annual reports shows but two articles over Hoadley's signature. During the same years the medical members of the board were, indeed, more active in discussing engineering topics than was the engineer member himself. The board, however, employed as consultants some of the outstanding civil engineers of the period, in particular James P. Kirkwood, who was the first American engineer to build a filtration plant for water purification, and E. S. Chesbrough, who was to become celebrated for his designs of some of the great sewer systems in the United States.

Investigations of the board that involved problems of chemistry were generally assigned to Professor William R. Nichols, of the Massachusetts Institute of Technology. Nichols, thereby, became the pioneer American water chemist. That the services of a chemist would be needed had been foretold, too, by Shattuck,[3] who wrote: "Many questions relating to the influence of the elements on the production or prevention of disease may require the special investigation of an experienced chemical philosopher, and this important branch of science should be ably represented at the Board."

It is a happy coincidence that in 1869, the year in which the Board of Health was organized, there was appointed as chief engineer of the Essex Company in Lawrence one Hiram F. Mills, then thirty-one years of age, for as we shall see the destiny of each was to be deeply influenced by the other. Mills was one of the first graduates of an American school of engineering, the Rensselaer Polytechnic Institute. He had worked with Kirkwood and also with Charles S. Storrow and James B. Francis, chief engineers respectively of the Essex Company in Lawrence and the Merrimack Manufacturing Company in Lowell. These men were the leaders of hydraulic engineering in the New World. With the examples of Francis and Storrow before him, Mills early determined to prepare a treatise on hydraulics, and set about gathering the necessary experimental information. When he became chief engineer of the Essex Company, which owns the dam and canal on the Merrimack River at Lawrence and controls the water needs of the manufactories, the opportunity presented itself to build a laboratory in which he could and did conduct his contemplated hydraulic researches. John R. Freeman, himself to become an engineer of distinction, was Mills's principal assistant for many years and has commented on "the rare devotion of Mr. Mills to the search for scientific truth and the deep insight, the untiring earnestness, and the consummate skill with which he carried on observations."[4] This talent for research Mills carried with him when he was appointed a member of the State Board of Health in 1886, a fact that is probably responsible for the remarkable service that engineers, chemists and biologists were able to perform for the Commonwealth under his leadership. Of Mills's association with the board, which had been reorganized in 1886 under the chairmanship of Dr. Henry P. Walcott, Freeman writes as follows:

> His profound interest and zeal as an investigator were then awakened to the importance of advancing scientific knowledge in matters of purification of public water supplies and of prevention of stream pollution, and for about twenty-eight years this work of one kind and another for the Massachusetts Board of Health, for which he received no pecuniary compensation, absorbed a majority of his time, to the neglect of his earlier investigations in hydraulic science. . . .
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> Later, when in partial retirement long after he had passed three score and ten years he resumed this earlier task, failing strength prevented his continuing these hydraulic investigations or discussions on the scope originally planned.[5]

Mills at the age of eighty years told Freeman with much feeling that he "had put off this work too long." Nevertheless he collected his many notes and from day to day, up to his eighty-fourth year, worked over them patiently and steadfastly as many hours as his strength would permit, declining the assistance of younger eyes and hands. Although he did not complete his notes for publication, they were made available to the profession by Karl R. Kennison,[4] now chief engineer of the Boston Metropolitan Water Supply, as a memoir of the American Academy of Arts and Sciences in 1924, three years after Mills's death.

But let us return to the memorable year of 1886. Along with the reorganization of the State Board of Health there was passed in that year a very important act of the Legislature, entitled "An Act to Protect the Purity of Inland Waters."

> Briefly, this act placed in the hands of the State Board of Health the general oversight and care of all inland waters, directed that examination of the waters be made to ascertain whether they were adapted for use as sources of domestic supply or likely to imperil the public health, and that recommendations be given as to the prevention of pollution. Authority was given to employ expert assistance, and to conduct experiments to determine the best practicable methods of purification of sewage or disposal of manufacturing refuse. The Board was also ordered to give advice to cities and towns, corporations and individuals as to sources of water supply and methods of sewage and refuse disposal, without expense to persons advised. Provision was also made for the submission to the Board of all plans and schemes in relation to water supply and the disposal of drainage or refuse, for its advice. And, finally, the Board was ordered to bring to the notice of the attorney general all instances of violation of the laws respecting the pollution of water supplies and inland waters.[5]

To carry out the provisions of this act, an engineering department was created in the State Board of Health, with Joseph P. Davis as consulting engineer, Frederick P. Stearns as chief engineer and X. H. Goodnough as assistant engineer. Davis had been chief engineer of the Cochituate Water Board,

the City of Boston and the Boston Main Drainage System, and so brought to his consulting work a wealth of experience. Stearns directed the Engineering Department during its formative years, and would probably not have relinquished his position to become chief engineer of the Metropolitan Water Board, which constructed the Wachusett water supply for the Boston Metropolitan District, had this enterprise itself not been one of the great projects of the State Board of Health. Goodnough succeeded Stearns in 1895 and, on his retirement in 1930, passed on the reins of the Engineering Department to the present incumbent, Arthur D. Weston.

Along with the development of an engineering staff, the Act to Protect the Purity of Inland Waters had made available funds for the systematic analysis of water. This permitted drawing into close association with the engineers a notable group of chemists and biologists, some of whom were on the faculty of the Massachusetts Institute of Technology, in whose laboratories the analytical work was performed until 1896, when a water laboratory was set up in the State House. In order to conduct experiments to determine the best practicable methods of purification of sewage or disposal of manufacturing refuse, Mills placed at the disposal of the State Board of Health his hydraulic laboratory at Lawrence, about which we have already heard. This laboratory was renamed the "Lawrence Experiment Station" and has continued its useful existence ever since. As a laboratory for sanitary research, this station was the first of its kind, and its influence on the progress of sanitary engineering cannot be overestimated. To staff the station, Mills drew heavily on young graduates of the Massachusetts Institute of Technology who had come under the influence of teachers who were then active in the chemical and biologic investigations of the State Board of Health.

Thus was initiated a decade of sanitary investigation the like of which has never been seen again in Massachusetts or anywhere else in the world. With the support of Dr. Walcott, and unified in their objectives by Mills's broad conception of what was needed in the task ahead, the Engineering Department, the Water Laboratory and the Experiment Station collaborated with imagination and zeal to initiate great engineering enterprises, lay the foundation for sanitary analysis and establish the experimental method as a means for determining the scientific and economic basis of public sanitation. The association of young men in this great adventure in sanitation appears to have been mutually so inspiring that there was to be hardly a man among them who did not make a significant contribution to the advancement of knowledge during his stay with the board and who did not, as well, make a name for himself in later life.

A list of these men would include among others the names of Thomas M. Drown, chemist, successor to Professor William R. Nichols at the Massachusetts Institute of Technology and later president of Lehigh University; William T. Sedgwick, biologist, later professor of biology at the Massachusetts Institute of Technology; Allen Hazen, engineer investigator, later one of America's greatest practitioners; George W. Fuller, chemist, who later at Louisville, Kentucky, laid the foundation for rapid sand filtration; Gary N. Calkins, biologist; later professor of protozoology at Columbia University; Edwin O. Jordan, bacteriologist, later professor of bacteriology at the University of Chicago; and Harry W. Clark, chemist, later director of the Water Laboratory and the Lawrence Experiment Station.

Notable among the great engineering enterprises of the group were the investigations that produced the Metropolitan Sewerage System of Boston, the Metropolitan Water Supply of Boston and the Charles River Basin, public works that satisfied the highest standards of engineering achievement and that continue to serve their intended function with success and distinction.

Many of the early studies of water purification and sewage treatment at the Lawrence Experiment Station are counted among the classics of sanitary engineering literature. Some of them, in fact, were so fundamental and so well conceived that they have continued to be reprinted in books on sanitary engineering for half a century. The Lawrence Experiment Station eventually became a mecca for engineers, chemists and biologists interested in the purification of water, the treatment of sewage and industrial wastes and the control of stream pollution. The visitors' book of the station is a veritable "Who's Who in Sanitation throughout the World."

The fundamental organization of state sanitation initiated in 1886 has continued up to the present time. The Department of Public Health has undergone two major reorganizations, those of 1914 and 1919, but the Engineering Division itself has pursued the even tenor of its ways with little deviation from its original aims and objectives except as expanding interests have brought new and varied problems to its staff for solution. In the course of time, the Engineering Division has built up a record of service and a background of legal justification that are unique in public enterprise.

The co-operation between the Engineering Division, the Water Laboratory and the Lawrence Experiment Station, which had been so fruitful during the early years of their existence, was allowed to become less close for a number of years. This worked particularly to the disadvantage of the Experiment Station, which lacked the challenge of engineering problems to be solved in practice. During this period some of its investigations appear to have been less well conceived and executed, as well as less productive of useful results. This situation was remedied some years ago, and there are signs that the station is on the way to recapture the fame and

usefulness that it acquired during its first score of years.

The powers of the Division of Sanitary Engineering have been advisory, in accordance with the general policy of the Department of Public Health. Only in times of severe stress has the "grammar of common sanitary legislation acquired the novel virtue of the imperative mood."[6] In this has probably lain the greatest incentive of the division for service. Throughout its existence, the counsel of the division has been sought as originally contemplated, and the record of applications for advice is one of steady growth. The construction of sanitary works in the Commonwealth has borne a direct relation to the activities of the division. This is exemplified by the progressive introduction of public water supplies. Prior to 1869 there were only seventeen such supplies in Massachusetts; by 1890 this number had increased to one hundred and thirty-eight; and by 1940 the 256 public water supplies of the Commonwealth served no less than 97 per cent of its total population. That these constructions were justified is shown by the declining annual death rate from typhoid fever. In 1873 this rate was 89 per 100,000 population; by 1890 it had dropped to 37, and by 1940 to 0.2.

Such is the story of engineering and its ancillary services within the Massachusetts State Board of Health. Needless to say, the work done has paid for itself over and over again in lives saved and sickness avoided, as well as in the general comfort and well-being of the people of Massachusetts. The influence of this pioneer engineering organization in a public-health department, however, has extended far beyond the borders of the State and, indeed, beyond the boundaries of the Nation. The published reports of the board became one of the most important sources for sanitary information, and young engineers trained in the Engineering Division carried its spirit and its methods with them when they left to join or organize the engineering divisions of other health departments, to take part in the design and construction of great sanitary works or to become teachers of sanitation in schools of engineering and schools of public health.

When Hiram Mills followed the injunctions of Lemuel Shattuck in his attack on the fundamental problems of environmental control by putting in requisition the services of other professions in their respective spheres, he created, in fact, a new and important discipline of public health as well as engineering and a career to be embraced by young engineers who, like Chadwick and Shattuck, could become enthusiasts for sanitation. Collaboration in sanitary research for the solution of basic engineering problems established above all the desirability of equipping engineers with a knowledge of chemistry and biology, and the study of these subjects has since become a heritage of sanitary engineers in America. The challenge that engineers could build disease or health into their works could either be turned aside by relegating responsibility for public-health decisions to other professions — as was done and has very largely continued to be done abroad, and I may add with less success — or it could be accepted by acquiring an adequate fund of information to be able to evaluate the public-health factors concerned. The engineers of Massachusetts chose to shoulder the responsibility themselves and so to play a significant part in the sanitary control of the human environment by engineering means.

After reviewing these contributions of Massachusetts to public health, I can find no more fitting expression for my own admiration of her accomplishments than is suggested by the last paragraph but one of Lemuel Shattuck's report wherein, after enumerating the many ways in which Massachusetts has stood for social progress, he says:[7]

> For these and very many other useful and honorable deeds, which might be specified, she has been named, by distinguished men of other states and countries, "the forefather's land," "the moral state," "the enlightened state," "the patriotic state," "the philanthropic state," "the leading state," "the pattern state," "the noble state," "the glorious old Bay State."

And may I be permitted to add, "the birthplace in America of public health and with it of the engineer in public health."

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

BENJAMIN CASTLEMAN, M.D., *Acting Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 31161

PRESENTATION OF CASE

A seventy-year-old retired dentist entered the hospital complaining of a painful swollen right knee.

Three years before admission the patient came to the Out Patient Department because of a stiff and painful back. At that time he gave a vague story of having had pain and stiffness in the right knee for several years. He was definitely relieved after strapping. Twenty-eight months before entry he fell forward to the ground while gardening. Soon afterward he developed pain in the right loin, radiating to the right thigh and leg. He was most uncomfortable while lying in bed. When examined twenty-seven months before entry the lumbar spine was rigid but not tender. The right knee was limited in extension to 15° flexion. X-ray studies at that time showed marked lumbar lordosis and extensive spurring of the lumbar vertebras, especially the third and fourth. There were marked osteophytes along the tibial joint surfaces of the right knee. Six months before admission he fell again, which caused stiffness and pain on motion in the right knee. He used a cane to get about. The pain and stiffness increased, and the joint became swollen. Two months before entry he began to use crutches. He had remained in bed for the past three weeks.

Physical examination revealed a thin, well-developed man. The right knee was limited in extension to 70° flexion, with approximately 15° of motion. It was swollen, brawny, warmer than the left knee and mottled red; it was tender and painful on motion. The heart was not remarkable, and the lungs were moderately emphysematous. A bifid coccyx was suspected.

The temperature, pulse and respirations were normal. The blood pressure was 170 systolic, 90 diastolic.

Examination of the blood revealed a white-cell count of 6000, with 68 per cent neutrophils, 22 per cent lymphocytes, 8 per cent monocytes and 2 per cent eosinophils. The urine was negative, the specific gravity being 1.012. The fasting blood sugar was 85 mg. per 100 cc., and the uric acid 4.1 mg.

X-ray films of the lumbar spine showed marked hypertrophic changes, with extensive spur formation and fusing of spurs between the third and fourth lumbar vertebras, as well as irregularity of the adjoining surfaces of the bodies. The abdominal aorta showed marked arteriosclerosis. An x-ray film of the right knee showed a marked change compared with the examination two years previously. Considerable destruction of the femoral joint surface was seen. A small fracture line appeared to extend through one of the condyles anteriorly. The joint space was markedly narrowed, and there was considerable soft-tissue swelling, with probable fluid in the joint. All the bones of the joint showed marked decalcification extending well into the condyles. X-ray films of the heart and lungs were negative.

The right knee was put into suspension traction, and the joint was aspirated. Thick pus-like synovial fluid was withdrawn, which contained 34,500 white cells, with 92 per cent polymorphonuclears, 3 per cent lymphocytes and 5 per cent monocytes, and 29,000 red cells per cubic millimeter; there was mucin but no sugar. The cell count was probably inaccurate because the purulent material did not mix well in the counting fluid. A culture showed no growth. The sedimentation rate was 24 mm. in 60 minutes. A tuberculin test in a dilution of 1:100,000 was positive, presenting an 8-mm. area of redness and induration. The serum calcium was 8.8 mg. per 100 cc., the phosphorus 3.3 mg., and the phosphatase 3.1 Bodansky units.

In the forenoon of the fifth hospital day the patient had a sharp transient precordial pain, which radiated at once to the back and then disappeared. A few minutes later he again had severe pain, became markedly dyspneic and pulseless and expired.

DIFFERENTIAL DIAGNOSIS

DR. FRIEDRICH W. KLEMPERER: It is obvious that the terminal episode had no direct correlation to the chief complaint that brought the patient to the hospital. I shall try to discuss the joint disease first.

From the history we learn that the patient was suffering from chronic joint disease involving the spine and right knee. The total duration of the illness is not given accurately, but it certainly was greater than three years. The distribution of pain in the low back and loin and the radiation to the thigh are characteristic of involvement of the lumbar spine. It is the rule to see disappearance of back pain after complete fusion has developed. The involvement of the knee had progressed gradually over the course of years, with an acute exacerbation caused by injury six months before admission. This history of chronically progressive arthritis leads us to a differential diagnosis between chronic infection, such as tuberculosis, and rheumatoid arthritis.

Primary bone tumor seems less likely at this age. Metastatic malignancy might be considered, but of course the story is somewhat long and we have no evidence of a primary lesion. Pyogenic infection

*On leave of absence.

also seems unlikely in view of the lack of acute symptoms as well as the duration. Could he have had a chronic osteomyelitis? I do not believe that this is likely, and the x-ray findings probably rule it out.

The physical findings are indicative of a chronic inflammatory lesion but do not rule out tumor. Again, an acute infectious process is ruled out by the absence of marked tenderness, redness and heat. The laboratory examinations are most helpful. First we hear that the aspirated knee fluid was pus-like and sterile. The fact that it was sterile is further evidence against pyogenic infection. A cell count of 34,500 may be seen in rheumatoid arthritis, although frank pus probably does not occur. Effusions due to tumor probably never show cell counts of this magnitude, and I am inclined to discard the diagnosis of tumor on that basis alone. The absence of sugar, frequently found in the presence of a high white-cell count, is often seen in tuberculosis. The elevated sedimentation rate is only a sign of active disease and not helpful in the differential diagnosis. A positive tuberculin test in a man of seventy is not diagnostic, but the violent reaction at a high dilution is in favor of the diagnosis of active tuberculosis. The phosphatase of 3.1 units serves to rule out such diseases as Paget's disease or tumor with osteoblastic activity. The x-ray films may be helpful.

Dr. Milford D. Schulz: These films taken two years prior to the last admission merely show pronounced proliferative changes. The joint space is quite well preserved (Fig. 1). Two years later the joint space is practically gone, the medial surface of the tibia is partially destroyed, and the bones are quite decalcified (Fig. 2). Although the knee had been painful for two years the decalcification of the femur is not too bad. The spine looks just like that of an old man.

Dr. Klemperer: Do you believe there is destruction in the area of the spine?

Dr. Schulz: There is a large spur on the side of one vertebra, and I wonder how much of what we see is not this spur projected upon the vertebral body. In the anteroposterior view one cannot trace the vertebral surfaces.

Dr. Klemperer: Are these areas of decreased density consistent with destruction?

Dr. Schulz: They did not change in two years, which is curious if they were due to active destruction.

Dr. Klemperer: It is obvious that at the time the first x-ray films were taken, two years ago, the patient presented the degenerative changes that a man of seventy is entitled to have, but I believe that there is also evidence of destruction in the spine. He had spurs completely bridging the anterior portions of the vertebras and causing complete immobilization of the spine. If this was tuberculosis, the fusion due to degenerative changes would explain the lack of progression of the lesion, in analogy to what we see after artificial fusion as a therapeutic measure. The diagnosis of a destructive lesion in the spine in addition to the apparent degenerative changes is also supported by the clinical symptoms. Severe pain is not usual in straight degenerative

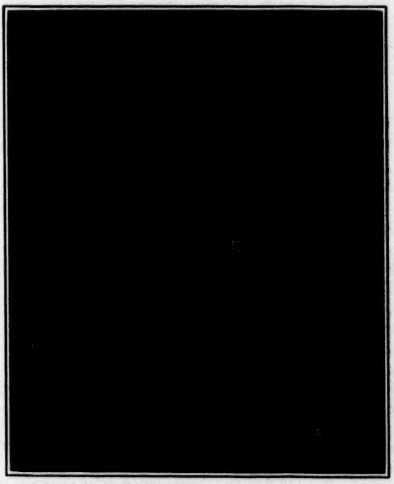

Figure 1. *Film of Knee Showing Proliferative Changes and Intact Joint Surface.*

disease of the spine and always requires another explanation, which in this case would be tuberculosis. The rapid progression of destruction and decalcification of the knee are also not consistent with a diagnosis of rheumatoid arthritis. I have never seen a patient with rheumatoid arthritis who had developed such extensive destruction in only two years without showing involvement of many other joints. I believe that rheumatoid arthritis remains a possibility although not a likely one. The rapidity of progression, the degree of destruction and decalcification of the bones around the knee joint, the localization and the character of the joint fluid are certainly best explained by a chronic infectious process, which in all probability was tuberculosis.

In discussing the terminal episode one must remember that observations made during the last few minutes of the patient's life, frequently by unexperienced observers, are notoriously inaccurate. The only thing one can say with a fair degree of assurance is that this man died an acute circulatory death. The most probable assumption in a man of this age who has been put to bed and whose leg has been kept in suspension is that he had developed a phlebitis of the femoral veins that led to a massive pulmonary embolus. He may also have died from acute coronary thrombosis. I admit that both these diagnoses, particularly the first, are the likeliest

ones on a statistical basis. The history, however, fits another condition so well that I should like to hazard a probable diagnosis of dissecting aneurysm. The patient had been known to have hypertension, and according to the roentgenogram, the aorta was markedly calcified. These two conditions predispose to the formation of a dissecting aneurysm. The story of sudden sharp pain with radiation to the back is particularly characteristic of this condition. The second attack of pain may indicate that at that time the aneurysm had dissected upward and had perforated the pericardium and that the patient died

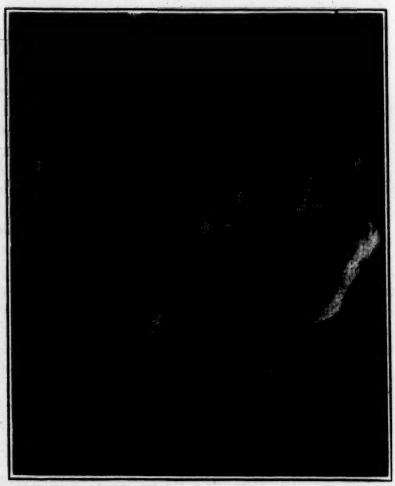

FIGURE 2. *Film of Knee Two Years Later Showing Areas of Bone Destruction and Soft-Tissue Swelling.*

of cardiac tamponade. I shall make this my first guess for the diagnosis of the final episode.

A PHYSICIAN: Does the fact that he had recurrent pain go against pulmonary embolism?

DR. KLEMPERER: I believe that that is against it.

CLINICAL DIAGNOSES

Suppurative arthritis, right knee.
Coronary thrombosis.

DR. KLEMPERER'S DIAGNOSES

Tuberculosis involving lumbar spine and right knee.
Degenerative joint disease.
Dissecting aneurysm of aorta?
Pulmonary embolism?
Coronary thrombosis?

ANATOMICAL DIAGNOSES

Tuberculosis of lumbar spine and right knee.
Massive pulmonary embolus.

PATHOLOGICAL DISCUSSION

DR. RONALD C. SNIFFEN: This man was killed by a massive pulmonary embolus. The fourth and fifth lumbar vertebras contained many small nodules of soft white material, but they were not compressed. The right knee was swollen, and the joint cavity was filled with yellow pus. The synovia was redundant and rough, and the articular cartilages of the femur, tibia and patella were partially destroyed. Sections of the vertebras and knee joint showed tuberculosis microscopically, and guinea pigs inoculated with material from the knee died of tuberculosis. The patient had no other signs of tuberculosis except for apical pulmonary adhesions.

CASE 31162

PRESENTATION OF CASE

First admission. A fifty-four-year-old shoe cutter was admitted to the hospital because of swelling of the abdomen.

One year prior to admission the patient developed a generalized itching unassociated with any skin lesion or jaundice. About two months later he noted increasing tiredness, although he was able to continue working. About six months before entry he noted swelling of the legs, brought on by standing for any length of time and disappearing after a night in bed. Soon thereafter he noticed that the abdomen was swollen and continued to enlarge, and a protrusion developed in the region of the umbilicus. Three months prior to entry he developed increasing dyspnea on exertion. A physician prescribed diuretic pills, following which the patient lost about 20 pounds in a few days. His abdomen, however, did not appreciably decrease in size. There was no history of gastric discomfort except for gaseous eructations after meals, and no hematemesis, melena or unusual stools. He had lost a "considerable" amount of weight over a period of six months.

The patient had been a rather heavy drinker of beer, augmented with whisky and rum, before the onset of his symptoms. There was no history of exposure to drugs and chemicals other than alcohol. He had had typhoid fever at the age of twenty. One and a half years before admission he had had a high-vein ligation in the right leg, and the veins of the left leg were injected at the same time.

Physical examination revealed a rather frail sallow man showing evidence of considerable weight loss. The lungs revealed fine moist rales at both bases, and diminished breath and voice sounds over

the entire chest. The diaphragm was high bilaterally. The heart sounds were clear, with splitting of both sounds and a questionable systolic murmur at the apex. The abdomen was markedly distended and tense, with shifting dullness and a fluid wave. A completely reducible umbilical hernia was present. No organs or masses were felt. A massive left scrotal hernia, completely reducible, was present. Both legs revealed evidences of stasis dermatitis. There was pitting edema of both feet, and induration of both legs to the knees. The knee and ankle jerks were not elicited, but other reflexes were normal.

The temperature was 98°F., the pulse 90, and the respirations 22. The blood pressure was 112 systolic, 70 diastolic.

Examination of the blood revealed a red-cell count of 4,300,000, with 12 gm. of hemoglobin, and a white-cell count of 7700, with 76 per cent neutrophils. The urine was negative. The serum nonprotein nitrogen was 31 mg. per 100 cc., the protein 5.6 to 6.8 gm., with an albumin-globulin ratio of 1.05, and the chloride 95 milliequiv. per liter. A bromsulfalein test showed retention of 30 per cent of the dye. A cephalin flocculation test was ± after twenty-four and forty-eight hours. Venous pressures taken in the antecubital space and femoral vein were equivalent to 18.5 and 14.5 cm. of water, respectively, on one occasion and to 20.5 cm. in both places on another. Fluid removed from the left chest had a specific gravity of 1.012, with a cell count of 1419 red cells and 138 white cells, of which 22 per cent were neutrophils, 76 per cent lymphocytes and 2 per cent eosinophils. Fluid from the abdominal cavity had a specific gravity of 1.014, with a cell count of 2610 red cells and 550 white cells, practically all of which were lymphocytes. The latter fluid contained 4.2 gm. of protein per 100 cc., and both the chest and ascitic fluids were negative for tubercle bacilli on smear and guinea-pig inoculation and for tumor cells. A sputum examination was negative for tubercle bacilli on smear. A blood Hinton test was negative.

A roentgenogram of the chest revealed a heart that was slightly enlarged but was within the limits of normal by measurement. There was a considerable amount of fluid in both pleural cavities. No liver shadow could be made out, and the hepatic flexure came almost to the diaphragm. The spleen was not enlarged. A barium swallow revealed a normal esophagus without evidence of obstruction or varices.

An electrocardiogram showed slight right-axis deviation. There were low-voltage QRS complexes and flat T waves in the standard leads.

The patient was placed on a high-calory, high-vitamin diet with fluids restricted to 2000 cc. daily. A peritoneoscopy was performed on the third hospital day. The right lobe of the liver presented a rounded edge that was just below the costal margin. The left lobe presented a rounded edge that extended down to the level of the umbilicus. The surfaces of both lobes were extremely irregular and in places hobnailed, and they were covered almost everywhere with innumerable white pinpoint tubercles. Some of these tubercles were seen on the peritoneal surface of the abdominal wall, overlying the left lobe of the liver. The transverse colon, small bowel and omentum in the upper part of the abdomen were involved in a red inflammatory mass in which there were a few tubercles. The lower abdomen appeared essentially negative. A biopsy specimen from the anterior surface of the left lobe of the liver showed no obvious abnormality.

On the tenth hospital day a paradoxical pulse was noted. and two days later a pericardial friction rub was heard. A fluoroscopic examination of the chest at that time revealed a small cardiac beat and no localized enlargement. There was no evidence of pericardial calcification, but there seemed to be some evidence of pericardial adhesions about the heart. The circulation time (arm-to-tongue) was 30 seconds. In spite of these findings, the patient continued to improve. He gained 15 pounds without significant accumulation of ascitic fluid and was discharged to his home on the thirtieth hospital day.

Second admission (two months later). Following his discharge the patient felt well except for persistent exertional dyspnea and some increase in abdominal distention. He gained about 10 pounds. He was readmitted for re-evaluation of his condition with a possibility of operation.

Physical findings were essentially unchanged except that a pericardial friction rub was no longer heard. The heart sounds were muffled. The pulsus paradoxicus was still present. The neck veins were pulsating and distended, there was considerable ascites and edema of the legs and feet, and the superficial veins of the abdomen were prominent. A roentgenogram of the chest showed no definite change.

Several chest and abdominal taps were performed, and the patient was given injections of Mercupurin to relieve him of some of the fluid.

On the twenty-eighth hospital day an operation was performed.

Differential Diagnosis

Dr. Conger Williams: The generalized itching without jaundice did not mean much to me in the light of what happened later, so I shall overlook it for the moment.

In the differential diagnosis of ascites, it is important to know whether or not there is leg edema and, if so, what the time relation of its onset is to that of the ascites. We are told here that swelling of the legs came on before the ascitic swelling was noticed. When the cause of ascites and leg edema is intra-abdominal, ascites develops first and

leg edema later, owing to pressure of fluid on the intra-abdominal veins. If, however, both are due to heart failure, edema of the legs commonly appears first. In the case of constrictive pericarditis, ascites is often out of proportion to the amount of leg edema and may appear first. In this case, the sequence of events is unusual for heart failure in that signs of peripheral congestion preceded dyspnea.

Obviously the diagnosis of cirrhosis of the liver was considered because of the history of alcoholism, but a search for esophageal varices was negative. The appearance of fluid in the legs before the development of ascites is also against the diagnosis. I suppose that the patient had varicose veins, but it does not say exactly why the vein was ligated. Obviously the injection was done for varicosities. Whether or not he had had thrombophlebitis, we do not know.

In brief, the cardiac findings on physical examination were not remarkable. Obviously the degree of ascites was out of proportion to the degree of leg edema.

We know nothing about the course of this man's temperature, either before or after admission.

In the differential diagnosis of edema, determination of the serum protein should be a routine procedure. The value of 5.6 to 6.8 gm. per 100 cc. is a little on the low side, but not low enough to be significant.

Thirty per cent dye retention in the bromsulfalein test is a moderately abnormal finding, but it is found in cases of simple liver congestion, without much in the way of parenchymal liver disease. Also, the cephalin flocculation test was equivocal, and can be explained on a basis of liver congestion alone.

The venous pressure readings were abnormally high, a finding of greater importance in making the differential diagnosis than any other reported physical or laboratory finding. I shall discuss it later in greater detail.

The characteristics of the abdominal fluid suggest an exudate rather than a transudate. The protein was high, the specific gravity was fairly high, and the cell count suggests more of a lymphocytosis than one expects from an ordinary bloody tap. So it is likely that a factor other than increased venous pressure was active in the production of ascites. The question of infection with tubercle bacilli is one of the most important things to consider in the differential diagnosis of ascites. A negative finding, however, especially on examination of the sediment of the ascitic fluid, means nothing. I think one can say that in tuberculous peritonitis one seldom gets a positive smear for acid-fast bacilli. Furthermore, it has been said that guinea-pig inoculations are positive in only about 50 per cent of cases. Thus, the negative findings in both these determinations mean little. Also, the fact that the sputum was negative for tubercle bacilli is of little consequence.

DR. LAURENCE L. ROBBINS: I have not been able to find the films taken on the first admission. I gather, however, that there was no change in the appearance of the heart or lungs. Someone made the statement that the heart was within normal limits of size by measurement. In none of these films is it possible to see the cardiac shadow sufficiently to be certain of it. This observation must have been made by the fluoroscopist. The fact that there was a small beat is of some importance.

DR. WILLIAMS: How about a large amount of pericardial fluid? Is that possible with this sort of right border?

DR. ROBBINS: It depends on how much you mean by a "large amount." There can be a lot of fluid in the pericardial cavity even with that configuration.

The lung fields are not remarkable. So far as I can see there is no evidence of disease in the lower and upper lobes, other than this linear fibrosis in the apices, which indicates a previous infection.

DR. WILLIAMS: Is this shadow the septum of the middle lobe?

DR. ROBBINS: Yes; with some fluid extending into it.

DR. WILLIAMS: These pictures are not particularly helpful, but I did not expect them to be. We know that he had fluid in the chest, because of the findings on physical examination and because of the fact that a goodly amount was withdrawn.

I saw the electrocardiograms, and the low voltage and the flat T waves are suggestive of pericardial involvement, which fits in later in the differential diagnosis.

I wonder whether the apparent hobnailed surface of the liver was related to the tubercles on the peritoneal surface. The record states that the biopsy showed no apparent intrahepatic disease. I do not believe that that means much one way or another. It is definitely stated, however, that tubercles were seen on the edge of the liver. The question I should like to raise is, Were these real tubercles or something simulating them? It is well known that widespread carcinoma may mimic tuberculosis, in the gross at any rate. We have no report of a histologic examination. I think it most probable, however, that these were real. The description of the transverse colon sounds like localized tuberculous infection in the abdomen.

A paradoxical pulse was noted. The question here is whether it actually appeared at that time or whether it was noted for the first time, having been present previously. It seems unlikely that a paradoxical pulse would develop so fast, unless there was a considerable amount of pericardial effusion. The x-ray picture suggests that the effusion, if any, was insignificant. Since there apparently was no great change in the blood pressure, and no sudden change in the clinical state, I am doubtful about the presence of pericardial tamponade. I suspect that pericardial involvement had been present for some time before the onset of symptoms, and that

the paradoxical pulse was also present long before it was observed for the first time. The friction rub suggests that there was acute inflammation of some part of the pericardium. Of course that often takes place in the presence of old pericardial fibrous changes. The small amplitude of heart beat may have been due to old pericardial adhesions. The absence of pericardial calcification means nothing in deciding on the presence of constrictive pericarditis.

It is quite likely that dyspnea at the time of the second admission, as well as on previous occasions, was due to an accumulation of fluid in the chest. Also, dyspnea is a symptom of constrictive pericarditis.

In describing a paradoxical pulse, the variation in systolic blood pressure between inspiration and expiration should be recorded. A good many normal people have a paradoxical pulse of slight degree, and it is often quite marked in bronchial asthma. The use of the term, "pulsus paradoxicus" without qualification is not especially helpful. In this case, however, the finding is significant, especially in association with distended and pulsating neck veins. The latter observation was not recorded until the second admission, but the high venous-pressure measurement suggests that visible venous pulsations in the upright position were also present at the time of the first admission.

I wonder whether the operation mentioned was an abdominal or thoracic procedure. Abdominal exploration is sometimes performed in tuberculous peritonitis. I suspect, however, that this was a thoracic operation and that it probably consisted of a pericardial exploration, because everything in the history points to a diagnosis of constrictive pericarditis — a high venous pressure in association with ascites, leg edema and the finding of a paradoxical pulse. Also the electrocardiographic findings are typical, and the absence of normal pulsation on fluoroscopic examination is suggestive. Also significant is the apparent absence of intracardiac involvement to explain the high venous pressure. I am therefore practically forced to accept the diagnosis of constrictive pericarditis.

The next question is, What is the relation of this to an apparent tuberculous peritonitis? Was the constrictive pericarditis also tuberculous, or was it the much more frequent nonspecific pericarditis, complicated by tuberculous peritonitis? It is more logical to suspect that the picture can be explained on the basis of a long-standing tuberculous constrictive pericarditis in association with tuberculosis of other serous surfaces, including the pleura and peritoneum. Tuberculous peritonitis alone does not explain the increased venous pressure and the findings in the lungs, unless one assumes that there was an independent tuberculous pleural process going on. We therefore must assume that something was going on outside the abdomen. One might say that the absence of fever and the increased white-cell count are perhaps against the diagnosis of tuberculous peritonitis, but we do not have a detailed record of the temperature. It is possible to have this picture caused by tuberculosis and at the same time to have a normal temperature. It is not usual, however, to have a high white-cell count in association with tuberculous peritonitis.

If this is tuberculosis, and it seems likely that it is, the next question that comes up is, Where was the original focus? So far as I can tell it was not in the lungs; perhaps it was in the mediastinum or elsewhere. It is true that cases like this usually have an obvious primary tuberculous focus. All I can say is that it just was not found.

Clinical Diagnoses

Polyserositis, with chronic constrictive pericarditis.
Bronchopneumonia.

Dr. Williams's Diagnoses

Tuberculous constrictive pericarditis.
Tuberculous peritonitis.

Anatomical Diagnosis

Polyserositis.

Pathological Discussion

Dr. Ronald C. Sniffen: I am sorry that Dr. White is not here, since he followed this patient rather closely through his medical career. Neither is Dr. Sweet, who performed the operation. Before he operated, Dr. Sweet made the remark that this type of case was most unfavorable for pericardiolysis, as judged from the experience of this clinic and others, because of the obvious activity of the process. But in view of the patient's continued downhill course he did operate and found a constrictive pericarditis. Thereupon he removed strips of the thickened pericardium from the anterior surface. After operation the patient did extremely well for a few months. It was seven months before he came in again, at which time he was in much the same condition as before operation. It is a little unusual for a patient to do so well postoperatively and then fail rapidly within a few months. Generally speaking, if the operation is not helpful there is no postoperative interval of improvement.

At the time of death the patient showed peripheral edema of the lower extremities to the knees. He had prominent neck and chest veins. In the distended abdomen there were umbilical and left inguinal hernias. The abdominal cavity was striking in that all the peritoneal surfaces were greatly thickened and appeared milky. This process involved the liver and spleen, and had produced adhesions around these organs. The serosa of the gastrointestinal tract was tremendously thickened,

but there were no adhesions between the various loops of bowel. The liver weighed 1980 gm. and, on section, showed a distinct lobular architecture and was quite tough. Microscopically the liver showed advanced central congestion and necrosis leading to an early cardiac cirrhosis. Each pleural cavity was largely obliterated by fibrous adhesions and contained about 100 cc. of fluid. There were also adhesions between the medial surfaces of the lungs and the pericardium. The entire pericardium was tremendously thickened, and the heart was fixed to the anterior chest wall and to the posterior mediastinal structures. The thickening was most impressive over the auricles, especially the right, where it measured as much as 1 cm. The orifice of the superior vena cava was narrowed to slightly more than 1 cm. in diameter. The orifice of the inferior vena cava, however, was capacious, measuring 3 cm. in diameter. The hepatic veins entering the inferior vena cava were not appreciably narrowed. The heart itself was not enlarged and revealed no intrinsic disease.

A blood culture and cultures of the fluid from the various cavities were negative, and guinea-pig inoculations were negative. Sections from the various serous surfaces showed a nonspecific subacute inflammatory process, with the laying down of many layers of collagen.

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CANCER

Again, April, by proclamation of President Roosevelt, is Cancer Control Month. During total war one might expect interest in cancer to assume a lesser place in one's thoughts than in times of peace; on the contrary, interest in it has rapidly increased. Perhaps the fact that cancer maims in an indiscriminate way on the home front and has killed more Americans since 1941 than has the war explains this phenomenon. The problem that cancer poses is formidable but by no means insoluble. As most members of the medical profession know, valuable new knowledge concerning cancer is being discovered daily and each bit of added knowledge solves or leads to the solution of some small part of the total problem.

For a long time the earnest workers studying cancer have been discouraged by the magnitude of the problem and the narrowness of the fronts on which it has been faced. In spite of generous gifts supporting cancer research, the total amount available is completely inadequate to make sufficiently broad studies.

Until recently, the efforts of the American Cancer Society have been in the fields of lay and medical education and in aiding the care of impoverished patients. This year for the first time, as previously mentioned in the March 22 issue of the *Journal*, the society is tackling the problem of supporting studies of cancer, in addition to increasing its unremitting efforts to spread present knowledge. A statement appearing elsewhere in this issue of the *Journal* describes this new departure in the society's affairs and its organization to an attempt to raise $5,000,000.

THE RH BLOOD FACTOR

The modern physician believes that mystery in medicine is as outmoded as is black magic. He is no longer afraid to tell his patients that he does not knaw a few of the secrets of the human body, and with him the aura of infallibility of a former generation is as obsolete as are its plug hats, its chin whiskers and its calomel measured on a knife blade. Medicine, today, is willing and eager to share its knowledge with its public. It asks only that all the facts be made known, that the case be temperately stated and that the hopes and the fears of human kind be not exploited in the interests of sensational journalism.

Too often, however, the newspapers and the magazines are a jump ahead of us and are peddling their borrowed wares on a bull market before most of us who should be best informed are ourselves thoroughly acquainted with the facts of the case. It is because of the half informed and poorly informed opinion that is already attaching itself to the mysteries of the Rh blood factor that the *Journal*

is presenting on other pages herein a thorough exposition of this recent addition to medical knowledge.

As recently as 1940, Landsteiner and Wiener, studying the agglutinins developed in certain experimental animals against the red blood cells of the rhesus monkey, found that approximately 85 per cent of human bloods contained an antigenic substance that was capable of reacting with this antibody. The agglutinogen was named the Rh factor, and bloods possessing it were called Rh+. Bloods lacking the factor were called Rh—. Persons with Rh— blood may become sensitized to the Rh factor by means of transfusions of Rh+ blood or, in the case of women, by bearing an Rh+ infant, the result of mating with an Rh+ man.

The practical importance of the Rh factor concerns Rh— women and their Rh+ offsprings, since, as has been stated, an Rh— person may become sensitized to Rh+ cells by an Rh+ transfusion, rendering subsequent Rh+ transfusions dangerous. Initial pregnancies with Rh+ infants may similarly sensitize the mother, producing in her blood agglutinins that will destroy the red cells of subsequent Rh+ infants, thus causing the anemia known as erythroblastosis fetalis; even the first infant of a mother who has been previously sensitized by one or more Rh+ transfusions may similarly suffer.

The inferences are obvious. Rh— persons should not receive repeated transfusions from Rh+ donors; Rh— women of child-bearing age should be protected completely against Rh+ transfusions because of the possible dangers to subsequent infants; and Rh— women mated to Rh+ men should, if one or more Rh+ children have been borne, be watched through subsequent pregnancies in order that proper measures may be taken to protect the infants.

An important point to remember is that the Rh factor, recently discovered although present for untold generations, is no cause for panic. In only about one fifteenth of the cases in which an Rh— woman is married to an Rh+ man is the infant likely to develop erythroblastosis unless Rh+ transfusions have been previously given to the mother, and less than one sixth of the infants so affected who recover suffer serious consequences in later life. As the author points out:

Since the placental barrier is assumed to hold back cellular elements, since some persons do not respond to Rh antigen by anti-Rh production, since 49 per cent of Rh+ men are heterozygous and can father Rh— children and since two or more pregnancies are usually necessary to produce infants suffering from erythroblastosis fetalis, this disease remains a fairly rare complication of Rh differences between mates. It may even be suggested that other incompatibilities between man and wife are more hazardous to married life than differences in the Rh factor.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON CANCER

The following statement signed by the Massachusetts members of the American Cancer Society is endorsed by the Committee on Cancer and recommended to the members of the Massachusetts Medical Society for careful study and action.

G. A. MOORE, *Chairman*

* * *

By the time this appears in print the medical profession and the public will have heard over the radio and seen in print many statements concerning the campaign of the American Cancer Society to raise $5,000,000 for cancer research and other aid to cancer patients. This society was formerly known as the American Society for the Control of Cancer. It was founded some forty years ago and has shown a steady, sound growth in activities and strength during this time. It has been particularly active in the fields of lay and professional education. During the last eight years its growth has been aided by the large number of members of its Field Army. This subsidiary organization has given devoted service in promoting cancer education and in providing financial and other aid to impecunious cancer patients. It is active in every state except Massachusetts, where the Department of Public Health carries on these activities in an efficient manner.

Although several foundations spend sums of money for the support of cancer research, the money available for organized research each year amounts to less than $1,500,000 for the country as a whole. On the other hand, cancer is killing over 160,000 people annually, and causing an expense and loss totaling many hundred millions of dollars. The officers of the American Cancer Society have long believed that this was not nearly enough support for a sufficiently broad study of this complicated disease and have secured the aid of far-sighted laymen in an effort to broaden the financial base supporting research on cancer and the care of patients with cancer. This lay committee is headed by Mr. Eric A. Johnston, president of the United States Chamber of Commerce, and the Executive Council is made up of distinguished men all over the country. Included are Mr. Robert Choate, publisher, *Boston Herald*, Mr. William K. Jackson, vice-president, United Fruit Company, and Mr. Sinclair Weeks, former United States senator and chairman of the Board of Directors, Reed and Barton. This committee ensures that the money-raising campaign will be well carried out.

Plans for spending the money raised provide for an equitable division of funds, with slightly more than 50 per cent to be allocated to the subsidiary state organizations, subject to approval of the parent society, and the remainder to the American Cancer Society. The bulk of the funds expended by the latter will go to cancer research in all its aspects, and some of the locally administered funds will also go to research. In addition, care of patients, facilities for treatment and many other cancer activities will be aided by increased support. That these activities will be efficiently carried out is indicated by the character of the officers, who are as follows: chairman of Board of Directors, Herman C. Pitts, M.D., consultant, Department of Cancer Research, Rhode Island Hospital, Providence; president, Frank E. Adair, M.D.,

chairman, Cancer Commission, American College of Surgeons, and surgeon-in-chief, Memorial Hospital, New York City; vice-president, Edwin P. Lehman, M.D., chief surgeon, University of Virginia Hospital and professor of surgery, University of Virginia Medical School, Charlottesville, Virginia; and treasurer, James J. Ripley, M.D.; and secretary, Eugene P. Pendergrass, M.D., director of radiology, University of Pennsylvania Hospital, Philadelphia. The Executive Committee is composed of these officers and the following: James B. Murphy, M.D., director of cancer research, Rockefeller Institute, New York City; Colonel C. P. Rhoads, chief, Medical Division, Chemical Warfare Service, and director, Memorial Hospital, New York City; Edwin B. Wilson, Ph.D., professor of vital statistics, Harvard School of Public Health, Boston; and John T. Morton, M.D., surgeon-in-chief, Strong Memorial Hospital, and professor of surgery, University of Rochester, Rochester, New York. Dr. Clarence C. Little, director of the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine, is managing director of the American Cancer Society, and Rear Admiral Charles S. Stevenson (MC), U.S.N. (ret.), is director of research.

To co-operate with the American Cancer Society, we, the physician members of the society who live in Massachusetts are forming a subsidiary organization. A layman's campaign committee has been appointed, with Mr. Arthur T. Lyman, of Westwood, as chairman, Mr. Ralph Lowell, of Westwood, as treasurer, Mr. Herbert T. Hand, Jr., of Boston, as director of publicity, Mr. George A. Baker, of Milton, as vice-chairman in charge of Greater Boston, and Mrs. William Brace Pratt, of Milton, as chairman of the Women's Division.

The American Cancer Society will welcome any aid that physicians can give to the success of this campaign. Doctors can well afford to give themselves and should urge their patients to give. Send a check today; do not wait for a solicitor to ask you for money because this year's campaign is so organized that personal solicitation cannot be made. Remember that you, in spite of being a physician, have as much chance of dying of cancer as any of your patients. This chance is one in eight for men, and one in five for women. Your money now may save your life later. An office has been opened at 186 Tremont Street, Boston, the telephone number being LIBerty 0240. Checks made out to the American Cancer Society may be sent to the above address or merely mailed to "Cancer," care of *your local postmaster*.

THOMAS ALMY
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MISCELLANY

"A SPOT ON THE LUNG"

Joseph Conrad once said, "A word carries far — very far — deals destruction through time as the bullets go flying through space." Medicine has a few such words. Too often these are used when a serious or potentially serious condition must be explained to an apprehensive patient. When words treacherously lull either the patient or the physician into a false sense of security, then words may ultimately maim or destroy as surely as if they were bullets. The following statement (Pinner, M. A spot on the lung. *N.T.A. Bull.* January, 1945) is pertinent.

* * *

It is futile to search in dictionaries or medical textbooks for a definition of the term "a spot on the lung." But the term is being used with great frequency by physicians, nurses and laymen alike. If this term is subjected to scrutiny, it is found that it may mean anything and everything that produces either a shadow or an area of decreased density in a chest roentgenogram or anything and everything that causes abnormal physical signs over the lungs. If, then, this expression has no meaning that cannot be stated more precisely in other terms, it remains to be found out why it is being used. If this is one of the terms that does not express a definite meaning, does it possibly obscure a meaning?

Nobody who has searchingly studied the histories of patients with pulmonary disease can doubt that the real function of the phrase, "a spot on the lung," is to cloud the facts. It is a cloak for a great variety of pulmonary diseases, a protective screen for the inability or unwillingness of the physician to arrive at a diagnosis acceptable to himself, a disguise for a bitter truth that the physician hesitates to tell the patient, an escape for the patient who tries to elude further diagnostic work and necessary treatment. After all, one does not die of "a spot on the lung," but one can die of bronchial carcinoma and one might die of pulmonary tuberculosis. Along with much other evasive, medical double-talk, "a spot on the lung" is a verbal mechanism of escape from reality. In the same category belongs the term "a touch of tuberculosis" and, improperly applied, "nothing but a little thickened pleura."

No physician needs to be told that "a spot on the lung" is no diagnosis. He realizes that it is evidence, on the one hand, of healed disease which calls neither for treatment nor for alarming its bearer, or, on the other, of active disease in need of treatment. The physician sometimes uses the term in patients in whom he has failed to establish, with a certainty that carries conviction for himself, the difference between active disease and obsolete scar. "A spot on the lung" has a pleasantly innocent sound. It lulls into inertia and indifference whatever doubts or curiosity the patient and, even in some cases, the doctor may have. But still it is, for the physician, a mental reservation. It seems to beckon as a safe place to stand if "a spot on the lung" later turns out to be carcinoma, tuberculosis or bronchiectasis.

Admittedly, this judgment may be harsh. But I dare say that it will be resented only by those who, with the instrumentality of this ambiguous term, neglect their obligation of persevering until "a spot on the lung" has been accurately diagnosed. No person need be told that he has "a spot on the lung." If the condition is as clinically insignificant as the term suggests, the patient should be told that he has a scar from a previous tuberculous infection — one that needs an occasional checkup or one that needs no further observation. Or when the diagnosis is certain, the patient should be told that his lungs are normal. For, while "a spot on the

The Journal lacks extra copies of the February 1 and March 8, 1945, issues. If any subscribers who do not bind their copies have the above-mentioned issues on hand, the Journal will gladly pay 15 cents for each copy left at or mailed to its office (8 Fenway, Boston 15).

lung" is often the obscured beginnings of destructive disease, it is, in other cases, the starting point for tuberculophobia and anxiety neuroses, conditions that are no less crippling and hardly more easily curable than tuberculosis itself.

But, though every reflecting physician knows that "a spot on the lung" is a meaningless and dangerous term, the utter convenience of the expression — and others like it — militates against their prompt extinction. Past experience justifies a pessimistic outlook. No amount and intensity of medical education are likely to eliminate entirely the term from medical parlance. Medical education, however, is being overtaken by the information that the public, including the prospective patient, is acquiring. People are learning to realize fully the confusing ambiguity of the term, they are beginning to refuse its acceptance just as an enlightened consumer protests against ambiguous and misleading labels on packaged goods. And the comparison is eminently proper: for all intents and purposes, "a spot on the lung" *is* ambiguous and misleading labeling. It may well be that through the protest of the consumer, by the refusal of every layman to be satisfied with the pseudo-diagnosis of "a spot on the lung" the term will eventually disappear.

It is high time for the medical and nursing professions and everyone engaged in tuberculosis work to bury a medical term that has quite literally buried so many patients. — Reprinted from *Tuberculosis Abstracts*, April, 1945.

CORRESPONDENCE

PENICILLIN THERAPY OF NEUROSYPHILIS

To the Editor: Following the use of penicillin for the treatment of early syphilis, there has been wide interest in its use in neurosyphilis. A study of this problem has been in progress at the Boston Psychopathic Hospital for over a year. Under the direction of the Department of Therapeutic Research of this hospital, working under contract with the Committee on Medical Research of the Office of Scientific Research and Development, Drs. Harry C. Solomon, Augustus S. Rose and Laurence D. Trevett have been treating cases of asymptomatic neurosyphilis, general paresis, tabes dorsalis, meningovascular syphilis, syphilitic optic atrophy and syphilitic meningitis. In some cases, malaria or fever-cabinet (diathermy) therapy has also been employed.

Physicians and clinics having such cases under their care are invited to send them to the Out-Patient Clinic at 74 Fenwood Road on Tuesday or Saturday morning from 8:30 to 10:00. A consultation will be held at that time, and arrangements will be made for the admission and treatment of suitable cases. There is no charge for the penicillin, and the ward rates for the patients are reduced in case of need. There are suitable wards for asymptomatic and other nonpsychotic cases. In each case, the welfare of the patient is the primary consideration.

HARRY C. SOLOMON, M.D., *Director*
Boston Psychopathic Hospital
74 Fenwood Road
Boston 15

CAUSE OF DEATH IN DIABETES

To the Editor: Everyone will welcome the article "The Cause of Death in Diabetes," by Drs. S. L. Robbins and A. W. Tucker, which appeared in the December 28, 1944, issue of the *Journal*. First of all, it again permits hope for those with diabetes, because the authors state that significant changes in the pancreas were observed in only 36 per cent of the 184 patients in whom the condition of the pancreas was noted. Von Noorden never saw nor have I ever seen a patient who was 100 per cent diabetic. Although the authors found significant changes in only 36 per cent of their cases, they did note some degree of change in the pancreas in an additional 6.5 per cent, which brings the total percentage of pancreatic lesions up to 42.5 per cent, as compared with the 74 per cent noted by Dr. Shields Warren.[1]

What enables one to make a diagnosis of diabetes post mortem must remain for pathologists to decide, but to me it hardly seems proper that this should be based solely on "glycogen nephrosis or so-called 'Armanni–Ebstein cells' in the tubular epithelium of the loops of Henle," because the authors frankly state that, with the passing years, the finding of glycogen nephrosis has become increasingly less frequent, suggesting that adequate therapy may prevent this type of secondary lesion. In contrast to the labile character of glycogen nephrosis, I should like to point out that hyalinization or fibrosis of the islands of Langerhans after it has once occurred does not disappear. Their criterion is of interest because of the recent article by Laipply, Eitzen and Dutra[2] on intercapillary glomerulosclerosis in which an incidence of 63.7 per cent of this type of lesion in diabetic autopsies is recorded and is used as their diagnostic criterion of diabetes. Robbins and Tucker, on the other hand, found intercapillary glomerulosclerosis, all degrees combined, in only 20 per cent of their cases. Such a seeming divergence of views is confusing to a clinician. I suspect that, if slides from 100 autopsies on diabetic patients were prepared and submitted to Drs. Robbins and Tucker, to Drs Laipply, Eitzen and Dutra and to Dr. Shields Warren, there would be far less difference of opinion than now appears to exist. It might also be advantageous in this connection to have an additional report on the diagnostic value of lesions of the kidneys in alloxan diabetes.

Coma as a cause of death occurred in a surprisingly small number of cases, there being but 22 in the 307 analyzed. Good as these figures are, I believe that, if the staff physicians of the Boston City Hospital now reviewed the treatment of these 22 cases, they would be able to state that, if these patients were to re-enter the hospital, the number of deaths could be materially reduced, possibly by as much as a half. That would be a worth-while study, and I hope that my suggestion will be considered constructive. Incidentally, it would be of interest to know the average age at death of the 22 patients with diabetic coma.

The authors draw comparisons between causes of death in the diabetic and nondiabetic groups, as recorded in their Table 1. There are similarities and differences that are of interest. Thus, vascular disease caused 35.2 per cent of the deaths in the diabetic group, and 27.1 per cent in the nondiabetic cases. It is interesting to compare the figures for these two groups with that for our group of 929 clinical cases.[3] Obviously, a sizable difference in any one item in one group will, other things being equal, force a consistent disparity in the others. Doctors Robbins and Tucker recognize this difficulty and call attention to it when they state that they threw the coma cases out of consideration. Furthermore, they explain the disparity in the percentages of coronary deaths in their two series and in the generally accepted clinical figure by the statements that their definition of coronary occlusion as a cause of death is quite precise and that "a certain percentage of acute coronary deaths are handled by the Medical Examiner's Office and hence are not available for inclusion within this series." In our clinical series, vascular disease was listed as the cause of death in 60 per cent of the cases.

Pulmonary infections in the diabetic series amounted to 25.6 per cent, and in the nondiabetic group to 24.2 per cent, as compared with 11.3 per cent in our clinical series.

Cancer was the cause of death in only 8.4 per cent of the diabetic group, as compared with 14.7 per cent in the nondiabetic group. This agrees with the 8.2 per cent in our clinical series, but the latter, however, is overweighted because of the influence of the numerous cancer cases in the Palmer Division of the New England Deaconess Hospital, which are included in our series. It is not at all surprising that the diabetic group at the Boston City Hospital showed a lower cancer death rate than did the nondiabetic group. It is true that the ages at death were the same, but the length of exposure to cancer of the diabetic patient is limited to the period that involves the duration of his diabetes and is quite different from that of the nondiabetic patient. In order to make accurate comparisons of this nature, what is needed, of course, is material by which one can compute death rates for the representative groups. If the higher mortality of the diabetic patient, as compared with the nondiabetic, were taken into account, many differences, on a percentage basis, would be wiped out; at the same time, those conditions to which the diabetic patient was prone would be thrown into even sharper relief. It might well be found, for example, that the cancer death rate was little different among diabetic and nondiabetic patients. All this indicates that, although this usual type of analysis is useful, one must keep in mind that the interpretation of such analyses should recognize its limitations. Furthermore, there is the fundamental consideration that there may be an association between the two diseases. This is discussed in detail by Wilson and Maher.[4]

Acute pyelonephritis as a cause of death was far higher in the diabetic series (7.3 per cent) than in the nondiabetic series (1.6 per cent). The incidence was only 1.7 per cent in our clinical series, but I am sure that the autopsied series is more accurate in this respect. With increasing apprehension we behold such cases after observing uncontrolled diabetes of about fifteen years' duration in young people, and I am positive that the danger of its occurrence should be emphasized One would like to know the sex of the patients. At one time we thought there was a predominance of females, but we have no analysis of recent data. I[3] have recently discussed disease of the kidneys in uncontrolled diabetes.

The incidences of tuberculosis were about the same in both autopsied groups, being 5.6 per cent for the diabetic series and 8.0 per cent for the nondiabetic. In our clinical series, tuberculosis was recorded as a cause of death in 3.6 per cent of the cases.

In their conclusions the authors state, "The diabetic patient lives as long as the nondiabetic." I wonder if they would wish to modify this sentence or in some way to reconcile their statement on longevity of the diabetic as compared to the nondiabetic patient. The former do not live so long as the latter. In our latest compilation, the average duration of the disease was 13.7 years, although 18.2 per cent of the patients lived over twenty years. In fact, the life expectancy of our diabetic patients is about two thirds as long as that of nondiabetic patients. The authors seem to have overlooked the facts that the usual figures for the expectation of life relate to the expectation at birth and that in referring to the expectation of life for diabetic patients one should take account of the age at which the diagnosis of diabetes was first made. Thus, Table 45 on page 279 of our book[3] shows the expectation of life for the general population and for diabetic patients according to different age groups. It was prepared with the co-operation of the Statistical Bureau of the Metropolitan Life Insurance Company and is based on death rates of each age subsequent to first observation, regardless of the duration of the diabetes. The table is as follows:

Expectation of Life for the General Population and for Diabetic Patients.

Age	Normal White Persons	Diabetic Patients
10	57	40
20	48	33
30	39	28
40	31	21
50	23	14
60	16	10
65	12	8

From the above table it will be seen that the expectancy of life for the diabetic patient is approximately two thirds that of the general population for each age group.

Among the valuable hints that the article contains is the statement, "The example of a cerebral hemorrhage found at autopsy as a cause of death in a case clinically diagnosed as a diabetic coma is a not infrequent occurrence." Speaking for the group of doctors at the New England Deaconess Hospital, we can confirm that statement. In fact, we are beginning to have almost as many cases sent into the hospital with an erroneous diagnosis of diabetic coma as there are cases of diabetic coma itself. We welcome such cases, because the patients are generally very seriously ill and therefore just the ones to be seperated promptly from coma cases by proper laboratory tests. A blood carbon-dioxide combining power of 20 vol. per cent or lower is a good differential standard and serves as the greatest common divisor among the symptoms and signs of diabetic coma. That one sentence in the article will, I believe, do a great deal of good, because it emphasizes the necessity for all hospitals to provide laboratory service for diabetic emergencies.

Elliott P. Joslin, M.D.

81 Bay State Road
Boston

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* * *

Dr. Joslin's letter was referred to Dr. Robbins for comment. His reply is as follows:

To the Editor: Dr. Tucker and I greatly appreciate Dr. Elliott Joslin's interest in our article. The point that the life expectancy of diabetic patients is only two thirds as long as that of nondiabetic patients is extremely valuable and well taken.

Two questions that were raised can be answered. The average age at death in the coma group of patients was 46.7 years. In agreement with Dr. Joslin's impression, females outnumbered males by a ratio of 2:1 in our series of patients dying of acute pyelonephritis. The total number of cases involved, however, appeared to be too small to warrant any conclusion regarding sex predominance in this disease.

S. L. Robbins, M.D.

Mallory Institute of Pathology
Boston City Hospital
Boston

NEED FOR PHYSICIANS IN VETERANS ADMINISTRATION

To the Editor: I desire to bring to your attention the need of physicians for Rating Board work in the Boston office of the Veterans Administration.

A rating board is an agency of the Veterans Administration composed of a medical member, a claims member (attorney) and an occupational member, who pass on claims for benefits administered by the Administration and evaluate the degree of disability resulting from disease or injury. The medical member of this board reviews physical examinations and medical records from various sources and advises the board on all questions of medicine and resulting disability. The work is sedentary in nature and is quiet and dignified in character.

The hours of employment are forty-eight hours per week. The basic salary is $3800 which, with the overtime now in effect, totals $4424 per year, less the necessary deductions for retirement and tax purposes. The work may be considered reasonably permanent in nature, and this office is interested in receiving inquiries from physicians meeting the requirements of Civil Service, which are essential to employment in a federal agency.

It would be appreciated if this need were brought to the attention of your readers, as I am certain, that with the present numerous vacancies for physicians in the Veterans Administration there is work for all who are qualified or interested in this type of employment, particularly that type of man who, with a good medical background, cannot, because of some physical impairment, engage in active general practice.

A. A. Doucet, *Assistant Manager*

Veterans Administration
Post Office Building
Boston 9

NOTICES

ANNOUNCEMENT

Dr. Jonathan Zonis announces the removal of his office from 300 Seaver Street, Roxbury, to the Asthma and Hay Fever Clinic, 10616 Euclid Avenue, Cleveland, Ohio.

BOSTON GASTROENTEROLOGICAL SOCIETY

The next meeting of the Boston Gastroenterological Society will be held in the Mallory Amphitheater, Pathology Building, Boston City Hospital, on Wednesday, April 25, at 12 m. Dr. Frank H. Lahey will discuss "Lesions of the Stomach, Duodenum and Jejunum."

(*Notices continued on page xix*)